REMARKS

Entry of the foregoing and re-examination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.111, are requested.

By the present Amendment claim 28 has been amended to recite that the solution contains a diastereoisomeric excess of "at least 75%" of (6S)-sodium-folinate or (6S)-potassium-folinate. Claim 29 has been amended to recite that the solution is "sterile" and by deleting the "filling" step. Also, claims 42 and 54 have been amended to recite that the solution is contained in vials or ampoules.

At the outset, applicants would like to express their appreciation for the courteous and helpful interview extended to the undersigned by Examiner Rao on July 23, 2010. During the interview, the aforementioned amendments were discussed, but no agreement was reached. The substance of the interview is accurately memorialized in the Examiner's Interview Summary dated July 29, 2010.

As discussed during the interview, and as now explained in the Declaration of Dr. Fabrizio Marazza (Appendix I), support for the recitation "at least 75%" of (6S)-sodium-folinate or (6S)-potassium-folinate can be found in Example 2 of the Specification (page 9). There it is stated that the starting material, i.e., (6S)-calcium-folinate, was prepared according to the methodology EP 600 460 and NO 172 492. As may be seen from U.S. Patent No. 5,489,684 (the U.S. counterpart to EP 600 460), that methodology will produce materials with a diastereoisomeric purity of at least 75%. Indeed, claim 1 of the U.S. patent recites (6S)-5,6,7,8-tetrahydrofolic acid with a diastereoisomeric purity of at least 75%. Example 1 (column 4, line 13) describes a material with a diastereoisomeric purity of 80.5%. And Example 2 (column 4, line 29) describes a material with a diastereoisomeric purity of 93%. Of course, and as explained

by Dr. Marazza, isomeric purity will not change during salt formation and storage. Therefore, it is clear that the inventors were in possession of, and disclosed, the invention as now claimed.

The claims stand rejected for a variety of reasons under 35 U.S.C. §112 and §101. It is believed that the aforementioned amendments should effectively address any concerns the Examiner may have relating to the clarity of the claims. Therefore, withdrawal of the rejections is requested.

The claims also stand rejected under 35 U.S.C. §103 based on the combination of *Buchs et al* (U.S. Patent No. 5,814,635) and *Mueller et al* (U.S. Patent No. 6,160,116). For the reasons that follow, these rejections should also be withdrawn.

As set forth in amended claim 28, the invention is directed to a concentrated, stable solution, comprising water and a diastereoisomeric excess of (6S)-sodium-folinate or (6S)-potassium-folinate. The (6S)-sodium-folinate or (6S)-potassium-folinate is in a diastereoisomeric excess of at least 75%.

Buchs describes a mixture of R and S diastereoisomers, i.e., "sodium-leucovorin or potassium-leucovorin or sodium-N(5)-methyl-5,6,7,8-tetrahydrofolic acid or potassium-N(5)-methyl-5,6,7,8-tetrahydrofolic acid both of which are in the racemic form (R and S)". As recognized by the Examiner, Buchs et al does not teach their concentrated folinate solution to comprise a diastereoisomeric excess of the 6(S) sodium-folinate or potassium folinate. In fact, the solutions of Buchs contain 50% of the inactive (6R) configuration. For this deficiency, however, the Examiner cites to Mueller et al for its method of preparing "pure" sodium (6S) folinate (see page 9 of the Action).

The combination of Buchs et al and Mueller et al would not render the presently claimed invention obvious. In particular, contrary to the assertion in the Action, Mueller et al does not disclose a method of preparing "pure" sodium (6S) folinate.

The claims call for solutions of (6S)-sodium-folinate or (6S)-potassium-folinate. As taught in the specification these solutions are prepared from *amorphous* (6S)-folinic acid (see also claim 29), which, in turn, has been prepared from (6S)-calcium-folinate (see also claim 30). As explained in the Specification, and verified in the attached second Declaration of Dr. Fabrizio Marazza (Appendix II), (6S)-folinic acid itself, much less (6S)-sodium-folinate or (6S)-potassium-folinate, could not be obtained following the teachings of the applied prior art. In particular, while Example 6 of EP 0 293 029 (the European counterpart to Mueller et al) seems to suggest that (6S)-folinic acid can be obtained by the careful addition of hydrochloric acid to an aqueous solution of calcium-(6S)-folinate, as detailed in the second Declaration of Dr. Fabrizio Marazza, following those teachings the applicants were only able to obtain an untreatable, rubber like product despite the fact that various parameters were varied such as temperature, concentration and reaction time. See also pages 2-3 of the Specification. Absent an enabling disclosure of a technique useful for obtaining the claimed solutions, the invention cannot be obvious from the combined teachings of Buchs et al and Mueller et al.

As noted in their last response, applicants are mindful of the legal authority suggesting that particular stereoisomers can be prima facie obvious from their racemic mixtures. See e.g., Sanofi-Synthelabo v. Apotex Inc., 2008 U.S. App. Lexis 24991 (Fed. Cir. 2008); Aventis Pharma Deutschland GmbH v. Lupin Ltd., 499 F.3d 1293 (Fed. Cir. 2007); Forest Labs Inc. v. Ivax Pharm. Inc., 501 F.3d 1263 (Fed. Cir. 2007). But that notion will not hold when, as is the

analogous case here, the isomers would have been difficult for a person of ordinary skill in the art to separate. *Id.*

Therefore, in view of the foregoing, it is respectfully submitted that the amended claims are patentable. Accordingly, withdrawal of all rejections and the issuance of a Notice of Allowance are believed to be next in order. Such actions are earnestly solicited.

In the event that there are any questions concerning this Amendment or the application in general, the Examiner is invited to contact the undersigned so that prosecution of the application can be expedited.

The Director is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-4047.

Respectfully submitted,
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